ANALYTICAL CHEMISTRY IN A GMP ENVIRONMENT

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A Practical Guide

EDITED BY

James M. Miller Jonathan B. Crowther

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SAFETY

The laboratory procedures described in this text are designed to be carried out in a suitably equipped laboratory. In common with many such procedures, they may involve hazardous materials. For the correct and safe execution of these procedures, it is essential that laboratory personnel follow standard safety precautions.

Although the greatest care has been exercised in the preparation of this information, the authors, speaking for themselves, and for the classroom and laboratory instructors, expressly disclaim any liability to users of these procedures for consequential damages of any kind arising out of or connected with their use.

The analytical procedures detailed herein, unless indicated as such, are also not to be regarded as official, but are procedures that have been found to be accurate and reproducible in a variety of laboratories.

APPARATUS

The items of apparatus described in this manual are intended to illustrate proper techniques to obtain a quality analysis and are not to be considered as official and/or required. Any equivalent apparatus obtained from other manufacturers may be substituted.

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CONTENTS

CONTRIBUTORS

Perlette Abuaf, IRI*Trials Management Center, Annandale, NJ, 08801

Sagar Adusmalli, Janssen Pharmaceutica, P.O. Box 200, Titusville, NJ 08560-0200

Henry Avallone, Janssen Pharmaceutica, P.O. Box 200, Titusville, NJ 08560-0200

Cindi Callaghan, Janssen Pharmaceutica, P.O. Box 200, Titusville, NJ 08560-0200

Jonathan B. Crowther, Janssen Research Foundation, Titusville, NJ 08560-0200

Jenny G. Feldman, Cilag A. G., Hochstrasse 201, 8205 Schaffhausen, Switzerland

Richard Hartwick, PharmAssist Analytical Laboratory Inc., Box 248A, South New Berlin, NY 13843

M. Ilias Jimidar, Janssen Research Foundation, Turnhoutseweg 30, B-2340 Beerse, Belgium

Ross Kirchhoefer, Gateway Analytical Laboratories, 5703 Hidden Stone Drive, Saint Louis, MO 63129

William Lauwers, Janssen Research Foundation, Turnhoutseweg 30, B-2340 Beerse, Belgium

Thomas Layloff, Division of Drug Analysis-FDA, 1114 Market Street, Room 1002, St. Louis, MO 63101

R. D. McDowall, McDowall Consulting, 73 Murray Avenue, Bromley, Kent, BR1 3DJ, UK

Harold McNair, Department of Chemistry, Virginia Tech, Blacksburg, VA 24061

Alvin J. Melveger, AJM Technical Consulting, 9 Patrick Court, Flanders, NJ 07836

James M. Miller, Department of Chemistry, Drew University, Madison, NJ 07940

W. Rorer Murphy Jr., Department of Chemistry, Seton Hall University, South Orange, NJ 07079-2694

Nico Niemeijer, Janssen Research Foundation, Turnhoutseweg 30, B-2340 Beerse, Belgium

Rudy Peeters, Janssen Research Foundation, Analytical Development, Turnhoutseweg 30, B 2340 Beerse, Belgium

Lee N. Polite, Axion Analytical Laboratories, Inc., 2122 North Bissell, Suite #3, Chicago, IL 60614

Paul Salomons, Janssen Pharmaceutica, P.O. Box 200, Titusville, NJ 08560-0200

Ponniah Shanbagamurthi, Janssen Pharmaceutica, P.O. Box 200, Titusville, NJ 08560-0200

Nicholas H. Snow, Department of Chemistry, Seton Hall University, South Orange, NJ 07079

FOREWORD

The laboratory is an extension of our senses, enabling us to obtain data on substances beyond what we can see with a naked eye and in amounts that our hands could never achieve. These data are compiled into reports and are ultimately used for making decisions, decisions that cannot be confirmed with our unaided senses. The quality of any decision is absolutely dependent on the quality of the data; junk data lead to junk decisions.

The process of acquiring valid data requires properly trained personnel using appropriately calibrated tools. In order to ensure the acquisition of high-quality data, one must be certain that all laboratory tools are suitable for their intended use [i.e., meet their standard operating procedure (SOP) requirements] within their validated limits. In addition, all involved personnel in the data gathering and information generation efforts must have the required knowledge, skills, and abilities (KSAs) to satisfactorily perform their tasks. As has been noted,* this is good business practice and, secondarily, necessary regulatory compliance.

In addition, however, our technological industry continues to churn out an ever-expanding array of almost magical analytical technologies, thereby creating a new group of incompetent laboratory personnel who are not familiar with or trained to use them.

Not surprisingly, these expanding technologies have posed a great and insurmountable challenge to our already much maligned educational system. The college/university curriculum continues with the traditional four-year program where the faculties are supposed to inculcate into the students the usual very strong foundation in the basic knowledge and skills of the science, packaged as a palatable academic program. Because all of this knowledge cannot be rationally delivered in a four-year curriculum, the assurance that those who generate data have the basic KSAs falls to the employers. Management must have confidence that all of the employees in the organization possess the required KSAs to perform their assigned tasks. As competent analysts performing in the laboratory reflect on the adequacy of the first-line management team, incompetent analysts in the laboratory reflect the inadequacy of that team.

Because of severe infractions in the practice of good science and science

* Alan Dinner, personal conversation.

management by several firms, the U.S. Food and Drug Administration found it necessary to issue regulations defining minimum appropriate standards for the performance of nonclinical studies submitted to the agency. This issuance of the "Good Laboratory Practices" regulations made the acronyms "GLPs" and "SOPs" "household" words in laboratories throughout the world. Subsequently, the agency issued the related regulations to provide administrative law guidance for pharmaceutical manufacture in the current good manufacturing practices (CGMPs).

In both cases the regulations were intended to provide broad guidance on appropriate scientific practices in the pharmaceutical industry while not stifling innovation and the evolution to superior practices that still satisfy the requirement. These regulations address many aspects of laboratory operations but only broadly address the skills and abilities of the primary practitioners: the management and bench scientists. This deficit was pointed out in "Analysts: The Unknowns in the Quality Assurance Equation".[†] That presentation and many subsequent ones focused on the fact that college science graduates do not in general have all the skills required to competently function in an FDA-regulated environment. This poses a crisis for first-line managers who must have absolute confidence that their staff members possess the required KSAs to competently perform the tasks that they are assigned.

In order to ensure that the scientists have acquired the required competencies to adequately perform their assigned tasks, management must establish quality systems structured to provide necessary training and education. It appears that one company, Johnson & Johnson, has taken a direct approach to meeting this challenge by establishing a laboratory analysts training and certification program for its employees.

This text has emerged from that program. It is designed to establish a basic knowledge and skill base in the technologies that are most prevalent in "product control laboratories" of the pharmaceutical industry. The laboratory supervisors who employ the individuals who successfully complete this course can have confidence that they have this well-defined starting point from which they may begin to evolve the individual employee's skills to journeyman performance levels in their specific organization.

THOMAS P. LAYLOFF

June 1999

[†] T. P. Layloff, AOACI Referee, December 1990, p. 6.

PREFACE

In his Foreword and elsewhere,* Layloff has described the need for more and better training of pharmaceutical laboratory analysts, as perceived by the Food and Drug Administration (FDA). To meet their own needs, the FDA produced a series of self-training aids that could be used in their testing laboratories. Many others are equally aware of the need for training because of the constant introduction of new methods, the increasing demands for better analyses, and the fact that little or no discussion of government regulations is presented in the traditional undergraduate educational program of chemists. Johnson & Johnson recognized this need in the spring of 1996 and began the development of an in-house training course. With the help of academic and industrial consultants, the course was first offered in October 1996 and became the basis for this text.

From the onset, the Johnson & Johnson Laboratory Analyst Training and Certification Program's (LATCP) objective has been to provide lecture and laboratory work in analytical chemical methods and in government regulations (CGMPs) and procedures. The two-week-long course has been presented over 20 times to over 300 analysts, selected from J&J sites around the world. A special facility was constructed for this purpose at the IRI Trials Management Center in New Jersey; more details on the program can be found in a recent trade publication.†

This book is a natural outgrowth of the LATCP and is being published to make the contents of the program available more widely. The level of the material is that which has been found suitable for the participants in the course, who, on average, hold bachelor's degrees in chemistry and already have some experience in the pharmaceutical laboratory; these are typical recruitment criteria for J&J analysts.

The introductory chapter provides an orientation to the drug development process that might not be familiar to new employees in the pharmaceutical industry. Two chapters follow on regulations and compendia. Together these chapters should serve as a basis for understanding the issues in this regulated industry.

* A. S. Kenyon, R. D. Kirchhoefer, and T. P. Layloff, *JAOAC Int.* **1992**, *75*, 742–746.

† N. Corkum, H. Avallone, and J. Miller, *Inside Lab Management*, *AOAC*, **2000**, *4*, 26–29.

The middle chapters cover some basics of analytical chemistry of relevance to this audience, beginning with statistics and a quick review of equilibrium and solution chemistry. While this material may be too elementary for some, we have discovered that many students in our course are deficient in basic concepts such as significant figures, so such topics are included. The major quantitative techniques covered next are spectroscopy (UV and IR), chromatography (GC, LC, HPLC, and TLC), and dissolution. Of these, HPLC is unquestionably the most important and is the focus of much of the material throughout the book.

The final chapters cover detectors (mainly chromatographic), quantitative analysis, and data systems, plus the special topics of method development (based mainly on HPLC), qualification of instruments, and validation and method transfer.

A multiauthor work such as this one runs the risk of being fragmented and uneven. We have tried valiantly to make it as unified as possible, drawing on our shared teaching experience with the LATCP course. It is, of course, impossible to define a single set of symbols when the topics are so diverse. Appendix I lists the terms and symbols used, noting overlaps in an attempt to keep confusion to a minimum. In chromatography, the IUPAC symbols are used, not those of the USP. This anticipates that USP will eventually adopt the IUPAC system in the spirit of unity and international cooperation. Other appendixes include the terms and some procedures used by another international group, ICH.

Being written to accompany the LATCP course, this book is intended for individual use by laboratory analysts. We have attempted to keep it as succinct as possible and provide sufficient detail, given the wide range of subject matter. The editor and the publisher welcome suggestions and comments for future editions.

We want to acknowledge the two persons who are most responsible for initiating and guiding this project: Hank Avallone, Juanita Hawkins and Nancy Corkum. Their vision, commitment, and support were crucial. In addition, we want to acknowledge the efforts of the LATCP Managers, Pat Magliozzi and Tom Caglioti.

Each of the authors is lauded for her/his efforts to produce a concise chapter within the limitations of time and page length. We also wish to thank the many content reviewers for their valuable time and expertise. Of course, none of this would have been possible without the tedious clerical support by IRI, especially Diane Kelly, Katherine Miles, and Patty Raymondi.

JAMES M. MILLER
JONATHAN B. CROWTHER

Madison, New Jersey
Titusville, New Jersey
March, 2000